Trans-NIDDK

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Trans-NIDDK
Table of Contents

7008 FUNCTIONAL GENOMIC TOOLS FOR THE STUDY OF THE ZEBRAFISH (RFA DK-98-006)
http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-98-006.html

FY 2002 Action
This initiative is being proposed as a trans-NIH effort complementary to the sequencing project expected to be undertaken by the Sanger Institute. This initiative is anticipated to involve the sixteen institutes that participate in the trans-NIH zebrafish coordinating committee, under leadership of the NIDDK and the National Institute of Child Health and Human Development (NICHD). The current proposal calls for continuation of NIH supported components.

Background
The zebrafish has become established as a powerful model organism, of value for the understanding of early vertebrate development, and for identification of genes responsible for organ formation and human diseases. Significant progress has been made in development of genomic tools for the zebrafish, largely through the support of the Trans-NIH Zebrafish Genome Initiative. Extensive mapping efforts by individual laboratories have produced a genetic map, currently anchored with nearly 4,000 independent simple sequence length polymorphisms, (SSLP) and 600 random amplified fragment length polymorphisms, (RAPDs). Nearly 2,000 genes have been placed on the map using restriction fragment length polymorphisms or single strand conformational polymorphisms. The NIH is currently funding projects to map additional genes and to place additional micro-satellite markers on the map. The SSLP map is coordinated with the RAPD map on an ongoing basis to ensure consistency and accuracy.

Two other funded projects focus on identifying and mapping ESTs. One is an EST sequencing project that has generated nearly 66,000 independent ESTs from various libraries, some of which have been normalized to reduce redundancy. Current plans include generating additional ESTs. The second project is to map an additional 5,000 ESTs onto a radiation hybrid (RH) map. Two independent zebrafish-mammalian RH panels have been developed for mapping of genes or EST sequences, and nearly 5,000 ESTs have been mapped on one of the panels, and 600 on the other. Some are mapped to both the meiotic (SSLP) map and the RH panel, anchoring the RH map to the genetic map and establishing syntenic relationships between zebrafish and humans.

There are additional genomics resources available, including BAC, YAC and PAC libraries, and a rich and growing collection of point, rearrangement and insertion mutants.

An informatics resource, ZFIN, has been established and is working to insure rapid access to all emerging information about the model organism. ZFIN informatics is associated with the Zebrafish International Resource Center, an NIH-funded stock center of zebrafish mutant and wild-type lines.

In summary, over the past several years, with NIH support, the zebrafish community has amassed a significant set of reagents and resources to enhance study of the genetics and genomics of the system. The community has created many of the tools necessary for positional and candidate cloning of mutant genes, thus establishing the basic infrastructure necessary to exploit the genetic power of this model organism. Reflecting

the recognized power of this model organism and the value of these resources, the Sanger Centre, with support of the Wellcome trust, is beginning a whole genome sequencing effort. The NIH anticipates working closely with the Sanger effort to avoid redundancies and assure complementarity of activities. The planned provision of whole genome sequence by the Sanger Centre will ameliorate many cloning difficulties, but only if the sequences can be assembled into long-range contigs, if it is well-annotated to identify genes, and if the functional tools to understand the underlying biology are available.

Research Goals and Scope

A. Continue genetic map development - Map an additional 2,200 genes and place enough additional micro-satellite markers on the map to yield, on average, one marker for each one cM interval.

B. Continue EST sequencing and mapping projects – Generate and sequence an additional 55,000 ESTs. Map an additional 5,000 ESTs onto an RH map.

C. Provide a scaffold for the sequencing efforts – Map the ends of BACs from a library onto the RH map. This will allow the Sanger Centre to physically position their sequence onto a map, and provide an independent scaffold to confirm their assembly of the sequence.

D. Support informatics efforts – provide funds for each project and for ZFIN to maintain excellent, publicly accessible, databases of genomics data with regular updates. Support efforts to correlate the genetic and RH and sequence maps, leading to the development of a single, authoritative, annotated map supported by independent lines of evidence.

7013 INNOVATIVE USE OF NON-MAMMALIAN MODEL ORGANISMS TO STUDY MEMBRANE TRANSPORT (RFA DK-01-012)

http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-012.html

FY 2002 Action

A trans-NIDDK initiative is proposed to develop tools and methods, which permit the exploitation of non-mammalian model organisms to characterize membrane transport processes.

Background

Abnormalities in membrane transport processes are associated with many human diseases, such as diabetes, cystic fibrosis, renal tubular acidosis, congestive heart failure (hypokalemia), and several intestinal disorders, which contribute to a major health care burden for the U.S. population. Many of these membrane transport processes are well conserved in lower organisms where the genomes are known, are genetically tractable, and are easily manipulated at the cellular and molecular levels. Thus, non-mammalian model organisms such as *Arabidopsis*, bacteria, yeast, *C. elegans*, *Drosophila*, and zebrafish offer ideal systems in which to understand the underlying mechanism, regulation, and protein structure of many evolutionarily conserved membrane transport processes.

Research Goals and Scope

To fully exploit these model systems, new experimental technologies need to be developed and/or existing technologies further refined. Therefore, this initiative will be designed to provide small grants (R21) to utilize non-mammalian models to develop reagents, methodologies, and novel approaches to the study of membrane transport, especially those involved in diseases of relevance to NIDDK. Examples include the development of isolated cell preparations and new cell lines (such as tubule cells) from genetically tractable organisms or organisms with sequenced genomes; development or refinement of electrophysiological, electron microscopic or imaging methods to be used for assessing membrane transport function and regulation in the intact organism; structure-function studies of purified homologous proteins or proteins in model membrane systems; the search for novel genes and proteins involved in membrane transport of ions and nutrients; and development and application of informatics tools for identifying membrane transport proteins and studying their function.

It is anticipated that, as a result of the grants funded with this RFA, new and innovative approaches will be developed and will be effectively utilized by the investigators to submit competitive investigator-initiated R01 research grant applications.

7018 HYPERACCELERATED AWARDS IN IMMUNOMODULATION TRIALS (RFA AI-01-001)
http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-01-001.html

FY 2002 Action
This RFA invites investigator-initiated research applications for mechanistic studies in clinical trials of immunomodulatory interventions for immune system mediated diseases, including, but not limited to, asthma and allergy; graft failure in solid organ, tissue, cell and stem cell transplantation; and autoimmune diseases. Specifically, this Request for Applications (RFA) is a continuation and modification of RFA AI-00-005. Proposed mechanistic studies associated with clinical trials supported by industry are particularly encouraged but clinical trials supported by any source, public or private, are eligible.

Background
At a workshop in December 1996, leading basic and clinical immunologists discussed the role the NIH should play in current and projected clinical trials for various immune mediated diseases. It was considered likely that clinical trials of many new immunologic interventions would be supported by the pharmaceutical/biotechnology industry. However, gaps in both knowledge and in research efforts were identified which represent opportunities for the NIH to contribute to progress in this area.

There was agreement that the mechanisms underlying immunologic interventions are poorly understood even in cases where efficacy has been shown (e.g., allergen immunotherapy and IFN Beta treatment for multiple sclerosis). In addition, clinical trials supported by industry and other sources including NIH often do not include studies of underlying mechanisms. There was consensus that high priority should be given to the utilization of patient samples from clinical trials in immunologic diseases for studies of the basic underlying mechanisms of therapeutic effect, immunologic function, and disease pathogenesis.

There was also agreement that the usual time required for grant review and funding is often incompatible with the time line of a clinical trial. Specifically, when a clinical protocol is finalized (which is required for applications submitted under this RFA), investigators are often ready to begin as soon as Institutional Review Board approval is obtained. The NIH was encouraged to develop a means of responding rapidly to opportunities to study underlying mechanisms in order to facilitate collaborations with industry-supported clinical trials. In order to review and confer awards to applications received in response to this RFA in a timely fashion without delay of the parent or core clinical trial, the National Institute of Allergy and Infectious Diseases has developed a pilot project in collaboration with the Center for Scientific Review. All applications responding to this RFA will be subject to this hyperaccelerated review/award process. Highly meritorious applications selected for funding under this RFA will receive their awards thirteen weeks after the application receipt date.

Research Goals and Scope
The objective of this initiative is to support mechanistic research studies in clinical trials of immunomodulatory interventions for immune system mediated diseases, including asthma and allergy, graft failure in solid organ and stem cell transplantation, and autoimmune diseases. Specifically, the goal is to utilize patients and patient materials

from such trials for the evaluation of immunologic and other relevant parameters in order to study the underlying mechanisms of the intervention, the mechanisms of disease pathogenesis, surrogate markers of disease activity and therapeutic effect, and mechanisms of human immunologic function. Such studies are not part of the parent or core clinical trial, and are commonly referred to as sub studies or ancillary studies. The parent or core clinical trial must have independent financial support and will not receive support under this RFA. Clinical trials supported by any source, public or private, are eligible.

7024 DEPRESSION IN DIABETES, RENAL DISEASE AND OBESITY (RFA DK-02-009)

FY 2002 Action
It is the purpose of this initiative to increase research on prevention and treatment of depression in diabetes, kidney disease, and other NIDDK related chronic diseases. It is also of interest to further studies that elucidate the role of depression in the risk for the development of diabetes, renal disease and obesity.

Background
Depression will be the second-leading cause of chronic disability worldwide during the first decades of the 21st century. Between 5 percent and 8 percent of the general population will have an episode of major depression at some time in their lives. Higher rates have been reported recently in younger individuals, predicting a worsening prevalence of major depression as the population ages. Major depression is a debilitating condition that impairs individual functioning and dramatically worsens quality of life. It is now recognized that 85 percent of depressed patients exhibit chronic recurrence of the disease, with each new episode bringing increasing likelihood of chronicity, functional impairment and suicide. Of great public health importance, depression is three to four time more prevalent in individuals with diabetes than in the general population, affecting 15 to 20 percent of patients with either type 1 or type 2 diabetes. Depression and diabetes as well as renal disease and obesity often occur together as co-morbid conditions**,** although one disorder can clearly be secondary to the other (such as depression developing as the result of life-threatening complications of diabetes). In addition, patients with chronic diseases such as diabetes not only have a higher incidence of depression, but these patients also have a high rate of recurrence following anti-depressive treatment and worsened health care outcomes. The cost in human suffering, loss of productivity and health care expenditures to the nation, as a result of both conditions occurring together, are magnified well beyond the cost of the individual conditions alone.

The co-morbid effects of depression on chronic disease outcomes have received relatively little research attention. Recent studies in patients with diabetes, however, have produced growing evidence that depressive disorders in adults are associated with worsened control of hyperglycemia. Treatment of depression using cognitive behavioral therapy in patients with type 2 diabetes has been shown to reduce the symptoms of depression and to significantly improve glycemic control. Similar findings were found in a small-scale short-term study using antidepressant medication. Patients with diabetes and with end-stage renal disease with depression are more likely to be hospitalized than patients with selected other chronic illnesses. Depression has been associated with increased mortality in patients with end-stage renal disease, but there are very few interventional or mechanistic studies in this population. This initiative will promote further research in diabetes, renal disease and obesity associated with depression.

Research Goals and Scope
A working group of experts in depression, diabetes, obesity and renal disease was brought together by the NIDDK and the National Institute of Mental Health to develop a strategic plan for identifying research opportunities in the co-morbidity of depression and chronic disease of interest to each of the participant Institutes. This was followed by a

conference held in January 2001, on Depression and Mental Disorders in Patients with Diabetes, Renal Disease, and Obesity/Eating Disorders. The Working Group and Conference recommendations called for increased research in a number of related areas. These include risk factors that increase the likelihood of co-morbidity and factors that are protective, the psychosocial and physiologic processes that contribute to co-morbidity and protection, and socioeconomic and racial/ethnic factors associated with increased risk.

The objective of this initiative is to initiate studies using the NIH research project grant (R01) award or the exploratory/developmental grant (R21) award mechanisms to focus on the co-morbid conditions of depression and diabetes, renal disease, or obesity.

7028 BIOENGINEERING RESEARCH PARTNERSHIPS

FY 2002 Action
This initiative invites applications for R01 awards to support Bioengineering Research Partnerships (BRPs) for basic bioengineering research addressing important biological or medical research problems. A BRP is a multidisciplinary research team applying an integrative, systems approach to develop knowledge and/or methods to prevent, detect, diagnose, and treat disease and understand health and behavior. The partnership must include bioengineering expertise in combination with basic and/or clinical investigators. A BRP may propose design-directed or hypotheses-driven research in universities, national laboratories, medical schools, private industry and other public and private entities.

Background
Many of today's biological problems are too complex to be solved by biologists alone; partners are needed in many disciplines, including physics, mathematics, chemistry, computer sciences, and engineering. Bioengineering integrates principles from a diversity of fields. The creativity of interdisciplinary teams is resulting in new basic understanding, novel products and innovative technologies. Bioengineering also crosses the boundaries of academia, science, medicine, and industry.

Recognizing the increasing importance of bioengineering in public health, the NIH established the Bioengineering Consortium (BECON) as a central focus for NIH bioengineering research. BECON held a two-day Bioengineering Symposium on February 27-28, 1998. The discussions and recommendations of symposium participants aided in the formulation of the BRP and Bioengineering Research Grant (BRG) initiatives. For example, both the BRP and the BRG recognize that applications for bioengineering projects are often focused on technology development rather than on proving or disproving a scientific hypothesis. Therefore, the NIH review criteria for bioengineering applications submitted in response to these initiatives have been modified to ensure that these applications are evaluated appropriately and fairly.

Research Goals and Scope
The goal of this initiative is to encourage research in selected basic bioengineering areas. Bioengineering is defined as follows: Bioengineering integrates physical, chemical, or mathematical sciences and engineering principles for the study of biology, medicine, behavior, or health. It advances fundamental concepts, creates knowledge from the molecular to the organ systems level, and develops innovative biologics, materials, processes, implants, devices, and informatics approaches for the prevention, diagnosis, and treatment of disease, for patient rehabilitation, and for improving health.

Each BRP should bring together the necessary engineering, basic science, and/or clinical expertise to focus on a significant area of bioengineering research within the mission of the NIH. A BRP can vary in size and exhibit diverse forms of organization, participation and operation. No single type of BRP fits the needs of every area. Rather, the size, structure and operation of a BRP are determined by the proposed research.

7030 MASTERS OF SCIENCE IN CLINICAL RESEARCH FOR MINORITY STUDENTS (RFA AR-01-009)

http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-01-009.html

FY 2002 Action

The NIDDK, National Center for Minority Health and Health Disparities (NCMHD), the National Center for Research Resources (NCRR), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Drug Abuse (NIDA), the National Eye Institute (NEI), the National Cancer Institute, the National Center for Complementary and Alternative Medicine, the National Institute of Allergy and Infectious Diseases, the National Institute of Dental and Craniofacial Research, and the National Institute of Nursing Research teamed to promote the first step in fostering the development of curricula in clinical research leading to a masters degree at minority institutions through RFA AR-00-009 for a one-year planning grant in FY 2001. This RFA (co-sponsored by NIDDK, NCMHD, NCRR, NEI, NIAMS, NIDA, the National Heart, Lung and Blood Institute, and the National Institute on Aging) is the second phase and invites minority institutions with professional schools offering doctoral degrees in one or more of the health care disciplines to apply for a clinical research education and career development grant. The purpose of this award is to support the development and implementation of curriculum-dependent programs in minority institutions to train selected doctoral and postdoctoral candidates in clinical research leading to a Master of Science in Clinical Research or a Master of Public Health in a clinically relevant area.

Background

As part of the effort of the Department of Health and Human Services to eliminate racial and ethnic disparities in health, a need has been identified to expand the training of clinical researchers at minority institutions as one approach to fostering careers in clinical research addressing health disparities. Minority institutions conduct high-quality programs for educating ethnic minorities, and they represent a rich resource of talent with the appropriate cultural sensitivity and perspectives needed in clinical research. However, minority institutions have had difficulties developing and sustaining independent clinical research, and there is a paucity of ethnic minority clinical researchers who are pursuing successful clinical research careers. There is a critical need for properly trained clinical researchers in certain health areas that disproportionately affect minority and underserved populations.

Research Goals and Scope

The award provides five years of support to a minority institution for a Clinical Research Education and Career Development (CRECD) program. The principal investigator leads a Curriculum Advisory Committee to design, develop, implement and evaluate a curriculum for an accredited Master of Science in Clinical Research or an accredited Master of Public Health in a clinically relevant area. The CRECD program must include a curriculum-based, multi-disciplinary didactic and collaborative training for clinical research and for collaborative clinical research experiences for trainees to enhance clinical research skills.

7033 DGAP—DIABETES GENOME ANATOMY PROJECT

FY 2002 Action
The proposed FY 2002 initiative would include all of the major organ systems affected by diabetes and its complications. The development of array libraries and bioinformatics tools applied to normal and pathological conditions of the endocrine, renal, cardiovascular, genitourinary, musculoskeletal, and peripheral nervous systems should contribute to our understanding of human physiology and spur development of diagnostic tools and therapeutic approaches aimed at reducing the burden of diabetes and its complications.

Background
Type 2 diabetes mellitus represents 90 percent of patients with diabetes in the U.S. In rare cases, such as Maturity Onset Diabetes of the Young (MODY), single genes have been implicated in the pathogenesis of this disease. However, most cases of diabetes appear to result from complex interactions between multiple genes and environmental factors. Major progress has been made in understanding basic insulin signaling pathways, glucose metabolism, and interactions between multiple tissues in the maintenance of glucose homeostasis and in the development of diabetes. Nevertheless, current approaches to this problem are inadequate to address the growing health burden of diabetes in a reasonable timeframe. Over the past decade the rapid progress of the Human Genome Project and extraordinary technology developments have led to an explosive growth in our knowledge of genetics and genetic basis of disease. Adequate resources are now available to apply a more systematic and coordinated approach to the complex problem of pathogenesis of diabetes and to develop more effective therapies for this disease. The NIDDK has initiated a functional genomics program, DGAP, which has initially focused on the endocrine pancreas and has as a major goal development of tools which are targeted to restoration of pancreatic beta cell function. This program involves a consortium of investigators at Washington University, the University of Pennsylvania, and Harvard University with expertise in pancreatic development, functional genomics and bioinformatics. This program will catalog all genes expressed in the developing mouse pancreas and make clones available through the IMAGE consortium. The Center for Bioinformatics at University of Pennsylvania, will soon release a web-based database which will contain tools to aid researchers in expression profiling, gene discovery, and promoter analysis. Microarrays developed by this consortium should prove valuable for studies of islet cell development, bioengineering of beta cells, and stem cell biology.

Research Goals and Scope
This initiative has three distinct aims:

1. Development of Reagents for Basic and Clinical Research: Tissue-derived cDNA libraries will be used to assemble a collection of expressed transcripts, including splice variants, for a large number of tissues of relevance to diabetes. As with CGAP, sequence data will be deposited in public databases. This approach is expected to yield a significant number of novel genes that may be important in the pathophysiology of diabetes or serve as potential drug targets. In addition, clones will be deposited in the IMAGE consortium for multiple distribution paths to investigators. While the purpose of this initiative is to construct comprehensive cDNA libraries and sequence novel genes, provision of gene profiling arrays to investigators is a long-term goal. A trans–NIH

committee of scientific staff, in consultation with the extramural scientific community, will develop a priority list of tissues relevant to diabetes as targets for this initiative. Likely candidates include kidney, adipose tissue, cardiovascular endothelium, muscle, liver, hypothalamus, and peripheral nervous and vascular tissue. (Note that pancreas is included in the ongoing program). Both mouse and human tissues will be used.

2. Comprehensive assessment of gene expression repertoire in major organ systems: Publicly available genetic sequence databases contain sporadic information about expression patterns of individual genes or expressed sequence tags other than original cell or tissue source. Dynamic information on changes in expression of every gene over a multitude of physiological conditions will tax our current bioinformatics systems. However, a simple annotation of the tissues in which a given gene is expressed under normal physiological conditions is feasible and would be of enormous benefit to the research community. This will require the construction of tissue specific libraries which represent a range of conditions to capture the gene expression repertoire of each tissue. Tissue libraries will be used as probes for existing microarray chips. This information can then be used to annotate Unigene (or parallel databases such as DOTS at U. of Penn.).

3. Development of Bioinformatics Tools for the Research Community: As more information is captured about patterns of gene expression in various normal and pathological states, the dearth of tools for basic and clinical investigators to apply to their specific research questions is becoming more apparent. No consensus appears to exist on a best approach to tap this vast reservoir of data. This initiative will encourage development of pilot query tools particularly directed at: (1) identification of potential drug targets; (2) identification of surrogate disease markers; and (3) understanding functional relationships between organ systems under various physiological and pathological conditions.

7040 MEDICAL STUDENT RESEARCH SCHOLARS (MSRS) PROGRAM (RFA DK-02-003)
http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-02-003.html

FY 2002 Action
This announcement invites applications for a National research Service Award (NRSA) Program developed to address the shortage of minority investigators trained in biomedical research. This program provides the opportunity for members of underrepresented minority groups who have completed at least two years of medical school and are currently enrolled, to gain research experience by contributing to or completing a research project in conjunction with one of the NIDDK-supported research centers.

Background
Available data indicate that there is a serious shortage of racial and ethnic minority physicians. There is an even greater shortage of health researchers from these groups. These physicians from racial/ethnic minority communities provide an invaluable service to patients who are minorities, poor and are Medicaid beneficiaries. It is essential that there be adequate numbers of physician researchers trained to focus on problems related to health disparities and bring incisive research to these areas.

This program is designed to attract students in the early stages of their medical careers; provide research training and mentoring with outstanding investigators actively engaged in biomedical research; and encourage the students to continue in a research career path once their medical school and clinical training has been completed. It is critical for the success of this program that the members of the training faculty, the administration of the medical school, and the training program director work together to identify, recruit and encourage those minority medical students demonstrating an interest in a research career to participate in the program. This will include outreach efforts, with the assistance of the staff of the recently created NIDDK Office of Minority Health Research Coordination (OMHRC), to interested students at minority-serving institutions where currently there are no NIDDK-supported centers.

Research Goals and Scope
The NIDDK supports P30, P50 and P60 Centers at 28 locations. To ensure that the medical students supported by the MSRS program are exposed to the highest quality research using the most-up-to-date equipment and cutting edge technologies, the NIDDK encourages the use of already funded, ongoing core facilities at the applicant institution. The training faculty recruited for the program should have access to these core facilities and most often will be members of one or more NIDDK-supported Centers. In addition, the trainees should be exposed to all of the enrichment activities organized and funded by the Centers.

7042 INFECTIOUS ETIOLOGY OF CHRONIC DISEASES: NOVEL APPROACHES TO PATHOGEN DETECTION (RFA AI-01-004)
http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-01-004.html

FY 2002 Action
The purpose of this Request for Applications (RFA), released February 14, 2001, is to solicit applications for research projects that propose developing novel technologies or improving established technologies to enhance the ability to identify and validate the role of microbial pathogens in chronic diseases and cancer for which an infectious etiology is suspected.

Background
Chronic diseases contribute significantly to worldwide morbidity and mortality. In the U.S., chronic diseases account for 70 percent of all deaths and 61 percent of all health care costs. Recent evidence indicates that microbial organisms play a role in the pathogenesis of a number of chronic diseases, including some cancers and a variety of cardiovascular, respiratory, gastrointestinal, and neurological diseases. Examples include peptic ulcers and gastric cancer (*Helicobacter pylori*), as well as Lyme arthritis and neuroborreliosis (*Borrelia burgdorferi*). In a number of chronic diseases an infectious etiology has been suggested. In Crohn's disease, *Mycobacterium paratuberculosis* or adherent *E. coli* have been suggested as potential etiologic agents. In colon rectal cancer *Streptococcus bovis* and schistosomes have been implicated as possible etiologic agents. Infectious agents may be involved in the pathogenesis of urologic and renal diseases such as nephrolithiasis, chronic prostatitis, and interstitial cystitis, and interstitial nephritis and immune complex renal diseases, such as various forms of glomerulonephritis. Infectious organisms have been implicated in the pathogenesis of a number of gastrointestinal and hepatic chronic diseases including ulcerative colitis, tropical sprue, necrotizing enterocolitis, celiac diseases, sclerosing cholangitis, biliary atresia, achalasia, autoimmune and cryptogenic hepatitis, acute liver failure and possibly obesity. In addition, viral agents have been suggested as possible triggers for an autoimmune process, which culminates in development of type 1 diabetes or immune complex renal disease in genetically susceptible individuals.

Research Goals and Scope
The purpose of this initiative is to stimulate research on the infectious etiology of chronic diseases and cancer and in particular, to focus on developing novel or improved technologies for the detection and identification of microbial pathogens in tissue samples from patients with chronic diseases and cancer. This research is critical for establishing an infectious etiology for chronic diseases and cancer, especially for those diseases for which an association with a specific pathogen is minimal, weak, or absent. This RFA encourages the use of recent technological advances in genomics, molecular biology, proteomics and computational biology to develop innovative approaches for pathogen detection and identification. Collaborative arrangements are also encouraged, in which scientists with expertise in epidemiology, pathology, clinical aspects of chronic diseases, molecular biology, computational biology, and genomic technology work together to apply innovative approaches for identifying the infectious agents in chronic diseases.

The search for an infectious cause of chronic diseases is particularly difficult when the organisms replicate slowly or not at all in culture, are present in low numbers, or are

present early or transiently in the disease process. Advances in DNA sequencing technology have allowed scientists to rapidly and efficiently sequence DNA of microbial genomes. Having access to the DNA sequence of entire microbial genomes has provided and will continue to provide an enormous amount of information about the microbe and facilitate the development of more sensitive and specific methods for universal analysis of microorganisms in biological samples. It is anticipated that genomic targets of microbial nucleic acid sequences or gene families can be used for pathogen detection in biological tissues. Host global gene or protein expression profiles, reflecting responses in the host to a particular infectious agent, also have the potential to provide novel approaches to microbial pathogen identification. The identification of a particular microbial pathogen as the etiologic agent responsible for a chronic disease will allow research to progress on studying the mechanism of microbial pathogenesis, as well as design of new treatment and prevention strategies for that disease.

Research topics of interest include, but are not limited to, the following:

- Development of novel or established approaches for wide screening methods for universal pathogen detection in biological specimens using, for example, sequence-based methods such as PCR technology and DNA microarrays, or emerging technologies that are designed for identification, quantitation and analysis of gene products and their interactions including mass spectrophotometry, protein arrays and biosensors.
- Validation of new and novel technologies for the identification and investigation of pathogens involved in chronic diseases and cancer. Representative studies for technology validation should include initial infection, and/or determination of etiologic role for new agents, and/or progression to chronic diseases and cancer.
- Development of innovative approaches to identify infectious agents in chronic diseases and cancer for which there may be a long interval between initial exposure to a pathogen and the subsequent development of clinically manifested disease.
- Development of improved techniques for subtractive hybridization methods such as representational difference analysis for identifying unique nucleic acids of microbial origin, including oncogenic viruses in biological specimens.
- Development of methods for studying the host response to infection from the microbial pathogen using state-of-the-art technologies for examining global gene or protein expression in the host cell, identifying possible diagnostic signatures that may distinguish infection by a particular pathogen and may include using genetically manipulated animals such as transgenic or gene knockout animals.
- Development of methods to isolate and express microbial and viral sequences that encode clinically relevant antigens leading to serological tests for microbial detection, as well as tissue immunochemical staining procedures.
- Development of bioinformatics tools to assist in facilitating pathogen identification in chronic diseases such as development of databases and software algorithms for processing and analyzing microarray data, genomic comparisons and DNA sequence or protein analysis for identifying gene families and protein structures such as antigenic sites and membrane proteins.

7044 and 7045 CENTER FOR INHERITED DISEASE RESEARCH (CIDR) EXPANSION AND GENOTYPING COSTS

FY 2002 Action

In FY 2001**,** the NIDDK joined the CIDR consortium for human and mouse genotyping. The CIDR genotyping facility proposes to double its capacity to perform genotyping since much of its present capacity has been committed. In order to accomplish this goal each supporting Institute will need to increase its contribution. Since we anticipate that several large genetic studies supported by the Institute will utilize CIDR genotyping, the NIDDK will expand its contribution to CIDR. Applications to use CIDR are reviewed by the CIDR Access Committee and the CIDR Board of Governors. The cost of genotyping for approved projects is charged to the Institute supporting the work at a rate of $0.50 per genotype. This initiative will provide funds to support genotyping projects across the Institute that are approved by CIDR in FY 2002.

Background

The Center for Inherited Disease Research (CIDR) is a centralized facility established at JHU Institute of Genetics to provide genotyping and statistical genetics services for investigators seeking to identify genes that contribute to human disease. CIDR concentrates primarily on multifactorial hereditary diseases although linkage analysis of single gene disorders can also be accommodated. CIDR was established in 1996 as a joint effort by eight Institutes at the National Institutes of Health (NIH). Currently, twelve Institutes support this effort. Mouse genotyping services were added in 2000.

Research Goals and Scope

Applications to use CIDR, should propose genome-wide scans to map diseases of interest to NIDDK including type 1 and type 2 diabetes, diabetic nephropathy, IBD, and obesity.

7048 REPOSITORY FOR MOUSE MODELS OF DIABETIC COMPLICATIONS CONSORTIUM (RFA DK-01-009)
http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-01-009.html

FY 2002 Action
In FY 2001, the NIDDK issued an RFA to establish a cross-disciplinary Mouse Models of Diabetic Complications (MMDC) Consortium that will develop innovative mouse models of diabetes complications that closely mimic human disease. The consortium will generate animal models that will be useful for the study of disease pathogenesis, prevention and treatment, and test the role of candidate genes or chromosomal regions that emerge from genetic studies of human diabetic complications, particularly diabetic kidney disease and accelerated cardiovascular disease. When a model is sufficiently characterized and validated, the mice will be distributed to the research community for individual investigator-initiated projects. The purpose of this initiative is to establish the required distribution systems to disseminate the mouse models to the research community.

Background
Recognition, prevention and treatment of diabetic complications is a central therapeutic problem in both type 1 and type 2 diabetes. In the U.S., diabetes accounts for 42 percent of all new cases of end-stage renal disease, 50 percent of all non-traumatic amputations, and is the leading cause of new blindness in people ages 20 to 74. More than 60 percent of people with diabetes are affected by neuropathy. Macrovascular complications are a major cause of morbidity and mortality in diabetes, particularly in patients with nephropathy. Diabetes also confers a markedly increased risk of developing oral complications. Because diabetic nephropathy does not occur in over half of patients with diabetes, and there is significant familial clustering of patients with diabetic nephropathy in the African American and Native American communities, there may be one or several susceptibility genes for diabetic nephropathy.

Genetic technology has advanced to the point that it is theoretically possible to genetically engineer mice that develop diabetic complications that are analogous to the major human complications of diabetes. Such accurate models of human diabetic complications would be especially valuable to analyze the initiation and progression of diabetic complications, to provide the framework for discovery of the genes and cellular parameters that generate susceptibility or provide resistance, to furnish targets for intervention and treatment, and to permit prevention, detection, therapeutic, and imaging strategies to be tested in the context of a normal tissue environment. Furthermore, it is now possible to more carefully phenotype both human patients and mouse models with unbiased techniques such as systematic gene expression.

Several well-characterized models of diabetes exist in the mouse; however, these mouse models have been used mainly to study the mechanisms for development of diabetes and the metabolic complications. In contrast, the pathogenesis of end-organ damage has received less mechanistic attention. Studies of complications have been largely descriptive—often reporting only histologic changes. Constraints of limited time and funding often do not permit an in-depth, comprehensive analysis and characterization of diabetic complications developed by these mice. Even fewer models are tested for their response to treatment or prevention modalities or their suitability for testing early

detection or imaging applications. The genes that confer susceptibility to diabetic nephropathy are unknown. The possible interrelationships between different complications (for example, neuropathy and macro or microvascular disease) that interact in diabetic patients have not been systematically studied in animal models. The NIH supports many individual projects that involve the derivation or study of mice that develop diabetes. However, at the present time, the NIH does not support a coordinated, collaborative effort to produce highly accurate mouse models of diabetic complications, particularly for the early design, derivation, characterization, and validation phases of model building, and to ensure that the models and the data relevant to them are readily available to the research community for further investigation or application.

Research Goals and Scope

The intent of this initiative is to assemble projects for a cross-disciplinary, multi-institutional MMDC Consortium whose component teams of investigators will refine or derive accurate mouse models of human diabetes complications. The approaches used for generating, characterizing and validating the mice for research purposes will reflect the blend of experience and creativity of the Consortium component groups, and will be originated by these investigators. The Consortium will validate the models for use by the research community for a variety of investigations, including for testing therapeutic, prevention, early detection, or imaging strategies, and assure their availability to the research community.

7050 CENTER OF EXCELLENCE IN GENOMIC SCIENCE (PAR-00-101)

http://grants.nih.gov/grants/guide/pa-files/PAR-00-101.html

FY 2002 Action

In collaboration with the National Human Genome Research Institute, the NIDDK will encourage development and application of analytical tools and approaches to identify gene-gene and gene-environment interactions responsible for the development of diabetes and obesity.

Background

In recognition of the increasing importance of biocomputing in biomedical research, the NIH has initiated a wide-ranging program to encourage the development of highly computer intensive analytical methods to problems involving large complex and multidimensional datasets and to encourage development of a cadre of scientists that can apply these tools to biological problems. Type 2 diabetes and obesity are diseases of very complex etiology with strong genetic and well as environmental components. The NIDDK has already initiated a type 2 genetics consortium to use linkage analysis to identify genes which confer increased susceptibility to type 2 diabetes. The completion of a working draft of the human genome and the identification of large numbers of single nucleotide polymorphisms (SNPs) through government-academia-industry partnership has provided tools which should be useful to identify disease genes. Recently, a gene associated with inflammatory bowel disease was discovered by scientists using this SNP library to assemble haplotypes to screen disease populations. This approach may have broad applicability to diseases such as diabetes.

Research Goals and Scope

Identification of genes which are associated with increased risk of developing diabetes would provide new therapeutic targets and, in addition, might provide tools to identify individuals at increased risk for the disease. Prevention programs focused on individuals who are at increased risk of developing diabetes may potentially be more cost effective and successful. The NIDDK should pursue funding of meritorious applications that propose to map SNP haplotypes in regions of the genome already implicated in diabetes, and to test the suitability of SNP haplotyping to the identification of genes associated with diabetes.

7051 NIDDK EXPANDED AWARDS FOR SBIR-AT-NIDDK (PA 01-093)
http://grants.nih.gov/grants/guide/pa-files/PA-01-093.html

FY 2002 Action
The NIDDK encourages the small business community to participate in the research and development of cutting-edge approaches, technologies, tools, methods, devices, cells, biomolecules and biomaterials that can be used in the study and/or treatment of diseases in the mission of the NIDDK. The NIDDK supports research pertaining to diabetes; endocrine and metabolic diseases; nutritional disorders, obesity, and digestive diseases; and kidney, urologic and hematologic diseases. Because the length of time and cost of research involving the development of advanced technologies may exceed those normally awarded for SBIR grants, this announcement serves to expand the allowable time and funding level requested for SBIR grants assigned to NIDDK (SBIR-AT-NIDDK).

Background
Advanced technology projects are defined as those that develop or employ high-cost new technologies or carry out high-cost, long-term toxicity or efficacy studies in animals, or clinical studies in humans. This program announcement is designed to allow increases in time and budget beyond the standard guidelines for SBIR applications for projects that develop and/or use advanced technologies in the study and treatment of diseases in NIDDK's mission.

Research Goals and Scope
This program announcement invites applications for SBIR-AT-NIDDK awards in the following areas:

- Identification, isolation, characterization and propagation of adult human stem/progenitor cells of the endocrine and exocrine pancreas, liver, gut, kidney, bladder, prostate, and hematopoietic lineages.
- Development of resources for progenitor cell research, including reliable and convenient clonogenic assays for progenitor cell populations in pancreas, liver, stomach/intestine, kidney, bladder, bone, and hematopoietic tissues.
- Development of broadly applicable methods for amplifying mRNAs from single or small numbers of recovered progenitor cells so that gene expression profiling can be performed, as well as protein profiling. Development of methods for manipulating gene expression in progenitor cells and their immediate descendents.
- Development of surrogate markers for identification of disease states, disease progression, and hepatotoxicity, or for use as endpoints in clinical studies of diseases within NIDDK's mission.
- Identification, generation and characterization of new receptor ligands and/or partial receptor agonists or antagonists with therapeutic potential for treatment of the diseases within NIDDK's mission. For example, use of rational drug design or high throughput screening methods to develop agents that interact with L-type calcium channels and can be used to treat diseases of the bowel.
- Development or application of imaging techniques to assess physiologic or functional changes in liver, kidney, gut, prostate, bladder or pancreas during disease progression or acute environmental insult to these organs. For example, the NIDDK encourages development of methods to measure pancreatic beta cell

mass, inflammation or perfusion; to measure iron content of the liver and to allow non-invasive detection of fibrotic, necrotic and fatty tissue in this organ; to measure progression of kidney disease; and to develop methods to differentiate between benign and malignant parenchymal diseases.

- Initiation and/or enhancement of research in tissue engineering for the development of pancreas or pancreatic islets, liver, gut and kidney. The NIDDK encourages research to ascertain angiogenic, adhesion or other factors necessary to promote the development of these organs or tissues *in vitro* and *in vivo*. In addition, the requirements of other types of cells must be examined. For example, endothelial cells or exocrine cells may synergize with the protein factors or endocrine cells to establish a pancreas or islet "organ" independent of or contained within the pancreas of a person with diabetes.
- Development of devices to aid in the diagnosis and treatment of diabetes, endocrine and metabolic diseases; nutritional disorders, liver and digestive diseases, motility disorders; and kidney, urologic and hematologic diseases. The NIDDK encourages development and testing of the following: non-invasive or minimally invasive methods of monitoring blood glucose; improved and miniaturized insulin delivery systems; integration of sensor and delivery systems to create an artificial pancreas (closed-loop system); devices to assess accurately energy intake and/or energy expenditure; and non-invasive measures of hepatotoxicity.
- Development of rapid and sensitive DNA chip technology and protein-protein interaction chip technology to help understand the physiology of disease conditions, and for ultimate use in the diagnosis and treatment of diabetes and other endocrine disorders, and diseases of the blood, kidney, genitourinary and digestive tracts, and their complications. For example, the NIDDK encourages the development of methods to do the following: measure the kinetics and levels of gene transcription and protein in beta cells, hepatocytes and cell populations present in the kidney, urinary bladder and prostate under different stimulatory conditions, or in disease states; correlation of gene and protein expression with disease progression in humans, non-human primates and rodent models of diabetes and obesity or during differentiation of progenitor cells into differentiated cell types such as a beta cell, hepatocyte, hematopoietic cells, prostate, urinary bladder and kidney.
- Development, propagation and distribution of novel genes, promoters and transgenic knock-out animals targeting processes involved in the development and/or function of pancreas, liver, intestine, urinary bladder, prostate, blood, and kidney.

7052 MEDICAL STUDENT RESEARCH TRAINING PROGRAM (Pilot Program)

FY 2002 Action

The NIDDK Medical Student Research Training program is designed to provide a mentored research training experience for those medical students who are considering an academic research career. Providing the opportunity for students to interrupt their medical school studies for up to 12 months to pursue a research project should help them solidify their decisions to pursue a research career, focus their research interests, and provide a background for future training and career development programs once they have completed their medical training. By linking the program to our NIDDK-supported Centers and training grants, we hope to provide the highest quality research and research training experience for this select cohort of students.

Background

Several recent reports have identified a steady, disturbing decline in the number of physician scientists engaged in biomedical research over the last decade. The development and implementation of the K23, K24 and K30 award mechanisms in FY 1999 and the legislated loan repayment in FY 2001/2002 are all aimed at reversing this trend. Should the numbers of physician scientists keep declining, the research areas supported by the NIDDK will suffer.

Currently, the NIDDK training programs concentrate on the support of physician scientists in their post-doctoral years. To address the issue of attracting more physicians into a career in research, we need to begin at an earlier career stage and pique the interest of medical students in pursuing a research career. The NIDDK currently supports ten short-term training grants, which provide funds for more than 200 medical students each year to devote two to three months to a research project while still in medical school. For those students who desire a longer research experience, we now wish to develop a program to provide support for medical students to interrupt their studies for a year while they participate in a research project. To ensure that this experience is a positive, productive, and motivating one, the program will be linked to our funded DK Centers. The reasons for doing this are several: (1) Centers have a strong, well funded, and ongoing research base; (2) Center members are encouraged, by virtue of the Center, to be highly collaborative; (3) Center cores provide the infrastructure necessary to ensure a enriching experience for the students(s); and (4) the environment within institutions with NIDDK-funded centers is enriched by Center supported seminars, visiting professors, and conferences.

Research Goals and Scope

NIDDK staff has identified six sites where the Institute supports Centers and training grants funded by each of three extramural funding Divisions. The Deans of the Schools of Medicine at these six sites will be contacted to invite their participation in this Medical Student Research Training program. The six identified schools are the University of Pennsylvania; the University of Michigan at Ann Arbor; the University of Washington, Seattle; Vanderbilt University; Washington University in St. Louis; and Yale. Funds will be provided to each of three medical students at each site *via* supplements either to one or more of the currently funded T32 grants at these institutions.

7054 NIDDK PROGENITOR CELL GENOME ANATOMY PROJECTS

FY 2002 Action

The purpose of this initiative is to solicit Cooperative Agreement Applications for Progenitor Cell Genome Anatomy Projects (GAPS) that will participate in the discovery of the processes necessary for development of tissue specific cells and organs from progenitor cells and the processes by which progenitor cells maintain and regenerate tissues and organs in health and disease. Because of the nature of the research questions, it is expected that potential applicants will include both investigators with expertise in the biology of progenitor cells and investigators having substantial expertise in bioinformatics. The components of the GAPS will work together as a consortium. It is expected that the consortium will serve as a resource to provide reagents and databases that will be made available to the research community.

Background

Genome Anatomy Projects (GAPs) have been established by the National Cancer Institute and NIDDK to accelerate the pace of discovery of genes expressed in specific tissues, such as tumors or the endocrine pancreas, and to exploit the sequence data emanating from the Human Genome Project. The GAPs foster the development of national networks of labs that characterize tissue-specific gene expression and identify novel transcripts. In addition, GAP researchers elucidate patterns of gene expression that lend insight into developmental programs and disease progression, and that may eventually be useful in diagnosis and treatment of disease. The bioinformatics systems associated with each GAP ensure that all of the data produced is available to researchers worldwide soon after it is generated in the laboratories. The NIDDK convened two working groups of its National Advisory Council to develop strategic plans for several cross-cutting areas of research, including stem cell biology and genomics. A joint recommendation of these groups was that NIDDK should catalyze a nationwide effort to characterize the molecular and cellular features of stem cells during and following development of the pancreas, liver, stomach and intestine, kidney and GU tract, bone, and hematopoietic tissues. This initiative should encourage development of comprehensive GAP programs that would combine development of genomics tools such as cDNA clones and microarrays with database platforms and tools to extract information from genome sequence, microarray data, protein expression datasets, image data (e.g., *in situ* hybridization) and other phenotyping techniques and apply these tools to progenitor cell research.

Research Goals and Scope

This initiative is intended to encourage programs to determine the gene expression profiles in the targeted stem or progenitor cell populations of human or murine origin and develop functional genomics tools to characterize the genes expressed. The relevant tissues for this initiative are developing and adult exocrine pancreas (the endocrine pancreas is excluded from this initiative), liver, stomach/intestine, kidney/bladder, bone and fat. Thus, all proposals must include separate sections describing each of the listed aspects of the project. Since stem cell research is at different stages of development for each of the targeted tissues or organ systems, it is anticipated that each project will allocate resources differently to the various parts of the GAP. Nevertheless, each proposal must include:

- Characterization and Definition of Cell Populations—Define and/or develop specific biomarkers, such as high-specificity antibodies or reporter gene constructs, for detection, classification, and isolation of stem cells and progenitors at multiple stages of development and differentiation, as well as those specific to particular lineages.
- mRNA Expression Profile—Profile mRNA expression in the relevant cell populations and identify novel genes and transcript splice forms specifically expressed in the targeted cell population using *in silico* methods, production and sequencing of cDNA libraries, as well as arrays and other methods.
- Histology and Functional Genomics—Develop rapid, sensitive methods for *in vivo* confirmation of patterns of gene expression. This phase of the project may also include the development of one or more gene-specific tools, such as reporter gene (e.g. with Green Fluorescent Protein, beta-galactosidase) and antisense constructs for characterizing the cell lineage under study and for analyzing the role of particular genes.
- Database—Although each GAP will develop its own database to store, organize, analyze, or visualize data, this database should be based on common modules developed by all the funded GAPs. The modules should include one that allows for Internet-based comparisons of progenitor cell gene expression data to similar data obtained from normal and diseased tissues from model organisms and humans.
- Research Tool Distribution—Develop and distribute to the research community well-characterized progenitor cells, cDNA clones, and high-specificity antibodies. In addition, the GAP should develop and distribute clone sets or long oligonucleotides for printing custom microarrays that can be used to identify and characterize the target stem cell population during different stages of development and differentiation. Similarly, the project should develop and distribute any functional genomics tools developed, including Green Fluorescent Protein (GFP) or antisense constructs, knockout cell lines or vectors for gene replacement, and other similar reagents that can be used to isolate and study the target cells at various stages and/or study the role of specific genes.
- Outreach—A major objective of this initiative is to disseminate the data and research reagents generated through each project to the research community as rapidly as possible. GAP programs should provide opportunities for long- and short-term training of researchers at all levels to take advantage of these data and reagents.

7056 DEVELOPMENT OF ZEBRAFISH MUTAGENESIS AND SCREENING TOOLS (PA-01-070)
http://grants.nih.gov/grants/guide/pa-files/PA-01-070.html

FY 2002 Action
This program announcement is a continuation of the program initiated by RFA HD-00-004, "Mutagenesis Screens/Phenotyping Tools for Zebrafish," that was issued in FY 2000 to encourage applications designed to exploit the power of mutagenesis screening in zebrafish. Studies are invited to detect and characterize genes, pathways, and phenotypes of interest in development, behavior, organ formation, disease processes and that propose to advance the technologies associated with mutagenesis screening. Strategies for mutation screening that would identify genes important for NIDDK interest areas such as metabolism, satiety, body temperature control, and digestive and excretory function are encouraged. This PA is a trans-NIH initiative with participation of sixteen Institutes, working though the Trans-NIH Zebrafish Coordinating Committee (ZFCC), under the co-chairmanship of the National Institute of Child Health and Human Development (NICHD) and the NIDDK.

Background
In the past decade, mutational screens in the non-vertebrate genetic models of the worm (*Caenorhabditis elegans*) and the fruitfly (*Drosophila melanogaster*) contributed significantly to our understanding of developmental pathways. These studies have led to the discovery of genes encoding signals, components of signaling systems, enzymes, and transcriptional regulators that act during embryonic development, often in complex cascades to regulate pattern formation, cell fate, and specification, as well as later events such as development of the eye, heart, and other organs. While these invertebrate systems have revealed much information and shown that numerous aspects of development are highly conserved among invertebrates and vertebrates, many features of patterning and organogenesis of the vertebrate embryo are distinct and cannot be studied in invertebrates. A complete understanding of human development will require experimentation in vertebrate model organisms. The study of mutations that affect development has been possible in the mouse, but the mouse embryo is not accessible *in utero* throughout much of its development. Consequently, mutational studies in this species have been limited largely to defects in postnatal maturation.

As a vertebrate, the zebrafish, *Danio rerio*, is more closely related to humans than yeast, worms or flies. It has a number of advantages as a model organism for study of vertebrate biological pathways. Many features of zebrafish development have been characterized, including early embryonic patterning, early development of the nervous system, and aspects of cell fate and lineage determination. The embryos are easily obtainable in large numbers and accessible throughout development; they are transparent, and undergo rapid morphogenesis, making them very amenable for phenotypic screens. In live embryos, the same specific cell or even cellular processes can, in many cases, be identified from individual to individual, affording a high level of precision in characterizing the effect of a developmental, environmental or genetic perturbation. The use of zebrafish to study vertebrate development, disease, and pathways of interest has been validated further by the demonstration that many of its genes show a high degree of structural and functional similarity to their human homologues.

The most powerful and unique feature of the zebrafish is that it is a vertebrate model organism in which large-scale forward mutagenesis screens can be performed with relative ease. Screens performed to date have focused exclusively on phenotypes in early embryonic development. Two large-scale screens have been performed, and the transparent embryos have been screened for defects in overall embryonic pattern morphogenesis. On May 10-11, 1999, the NIH sponsored a workshop entitled "Genomic and Genetic Tools for the Zebrafish." At this workshop zebrafish researchers were asked to help prioritize the short- and long-term needs of the community. A high priority emerging from this workshop was the recommendation for support of additional genetic screens, particularly screens focusing on later developmental events and on phenotypes in adult fish. The purpose of this initiative is to provide further support for zebrafish mutagenesis and phenotypic screening efforts.

Research Goals and Scope

The objective of this PA is to broaden the range, power, and utility of screens for new mutants of zebrafish. It will, therefore, support proposals for development of improved or novel methods for mutagenesis screens, as well as proposals for the actual execution of such screens. Objectives to be addressed in applications submitted in response to this PA include, but are not limited, to the following: (1) development and/or application of novel phenotypic screens based on observation of alterations in morphology, physiology, or behavior of mutants; (2) development and/or application of novel methods of mutagenesis; (3) genetic screens focusing on identifying mutations that affect the structure and function of specific tissue/organ systems; (4) screens to analyze the genetic basis of adult phenotypes including behavior, aging, organ disease, cancer, and responses to environmental toxins and drugs; (5) screens to detect altered gene expression patterns as a tool to identify components of genetic pathways or those altered by environmental agents; and (6) sensitized screens, using strains carrying a known mutation, in order to identify extragenic suppressors or enhancers of that mutation.

NIDDK is interested in research on diabetes, particularly studies on pancreatic beta cell function and development, obesity and mechanisms underlying satiety, other endocrine, and metabolic diseases, hematologic disorders, and diseases of the digestive system, liver, kidney, and urinary tract. Studies aiming to clarify the cellular and molecular events that dictate tissue and organ formation in these systems are considered of relevance. These studies could include, but need not be limited to, studies to develop cell lines from any of the tissues or organs of interest, studies to characterize normal or abnormal function of tissues or organs of interest, methods to screen and identify additional mutations in these systems, and studies to define the molecular mechanisms that dictate cell-specific gene expression in relevant cell types.

7057 PARTNERSHIP RESEARCH TRAINING AWARD (PRTA)

FY 2002 Action
This Request for Applications (RFA) invites faculty of universities to establish a collaborative partnership with NIH intramural research programs to pool a broader range of resources and faculty expertise in the areas of: (1) bioinformatics and computational biology; (2) neuroscience and neuroimaging; (3) human genetics and genetic-based diseases; (4) structural biology; (5) virology and infectious disease; (6) developmental biology; and (7) molecular epidemiology.

Background
The NIH intramural research programs are a rich source of scientific talent, resources and state-of-the-art research. Many postdoctoral research fellows are able to take advantage of these resources. On the other hand, graduate students are much less able to use NIH intramural research programs, in part because the NIH is not a degree-granting institution. One way to enhance the opportunities of graduate students to utilize the NIH intramural research programs as a valuable research training experience is to foster the development of formalized collaborations between universities and the NIH intramural programs.

Research Goals and Scope
The purpose of this RFA is to stimulate and support partnerships between universities and the research training programs of the NIH for the collaborative training of predoctoral students. A two-phase collaborative program combining funding from the NIH extramural National Research Service Awards (NRSA) followed by the NIH Intramural Research Training Awards (IRTA) will support the training of students over a five-year period. Predoctoral graduate students will be funded by the NRSA in phase I during the first year(s) of course work at the university and in phase II by the IRTA mechanism while at NIH. Universities are invited to submit applications for this Partnership Research Training Award (PRTA) for support of graduate student training leading to the Ph.D. University faculty will work with NIH intramural researchers to enhance research training opportunities for individuals who will train for careers in specified areas of biomedical research at both the university and the NIH intramural laboratories.

This new initiative will augment and strengthen the research and training capabilities of faculty and students at universities and the NIH intramural programs by supporting the development or enhancement of basic science, translational and clinical research doctoral degrees. This area is of high priority and significance because of its critical importance to the Nation's future researchers.

7058 PATHOPHYSIOLOGIC MECHANISMS OF OBESITY-ASSOCIATED CARDIOVASCULAR DISEASE

FY 2002 Action
The purpose of this initiative is to stimulate new research approaches to clarify the biologic basis of various obesity-related cardiovascular diseases, including atherosclerosis, cardiomyopathies, heart failure, arrhythmia/sudden death, and sleep-disordered breathing (sleep apnea). Funds would support basic and clinical mechanistic studies and the development of needed research resources.

Background
The adult U.S. population, whose prevalence of overweight and obesity now exceeds 50 percent, is experiencing a mass exposure to obesity-related cardiovascular risk factors and will suffer the inevitable clinical consequences in years to come. Also alarming are the ever-rising rates of overweight and obesity in children and adolescents. Increased rates of non-insulin dependent diabetes mellitus (type 2 diabetes) and evidence of increased risk of hepatic damage in overweight adolescents make it clear that children are not protected from the metabolic perturbations that accompany excess adipose tissue stores; we do not know what the consequences might be for a still-developing cardiovascular system if obesity is present during growth and maturation.

Overweight or obese individuals experience greatly elevated morbidity and mortality from nearly all of the common cardiovascular diseases (stroke, coronary heart disease, congestive heart failure, cardiomyopathy, and possibly arrhythmia/sudden death). This is partly attributable to co-morbidities (type 2 diabetes, insulin resistance, hypertension, dyslipidemias, and sleep apnea). The residual independent effects of obesity on cardiovascular risk, however, also suggest a role for less well-characterized mediators such as sleep-disordered breathing and other causes of chronic sleep loss. Because primary treatment and prevention of obesity often fail or are only partially successful, there will be increasing demands to treat the cardiovascular conditions attributable to obesity. In order to develop rational therapeutic approaches, it is necessary to understand the basic biology of obesity-related cardiovascular disease.

Emphasis will be placed on linking current knowledge of adipocyte and adipose tissue metabolism and function with cardiac and vascular biology or sleep regulation. Major areas needing further research and clarification include: (1) the role of adipose tissue as a proinflammatory secretory organ affecting multiple components of the cardiovascular system (e.g., blood pressure, lipid metabolism, vascular reactivity, myocardial metabolism, and clotting and inflammatory pathways) at every level of biological organization; (2) lipid infiltration (i.e., lipotoxicity) as a novel pathophysiologic mechanism; (3) cardiovascular, respiratory, and sleep neurobiology during obesity; (4) the impact of excessive adipose tissue burden on the final maturation of the cardiovascular system in young animals; (5) the specific pathophysiology of obesity cardiomyopathy; and (6) complex interactions between chronic sleep loss, hypertension, insulin resistance, and other endocrine dysregulation syndromes.

In addition, important knowledge gaps continue to exist for many “classical” risk factors, as well. For example, the exact mechanism by which hyperinsulinemia contributes to cardiovascular disease is not well understood, but it cannot simply be explained by an

association between insulin resistance and other known risk factors (e.g., dyslipidemia). Innovative approaches to understanding the molecular mechanisms by which insulin resistance and hyperinsulinemia cause endothelial dysfunction will contribute to understanding the pathophysiology of obesity-associated cardiovascular disease.

Research Goals and Scope

Novel experimental approaches taking advantage of the cardiovascular and respiratory dimensions of genetic and experimental models of obesity would be encouraged. New animal models are needed, including immature and growing animals. Distinct lean and obese phenotypes, and other well-defined intermediate phenotypes, in humans and large animals also may have high utility for mechanistic studies. In addition, new methodologies such as microarray technology and targeted gene expression may help speed the search for markers that predict disease, track its development, or influence treatment outcomes.

The budget for this program is structured to provide funds primarily for regular research project grants. In addition, it is envisioned that several projects could encompass the development of resources needed to advance the field; these resources would be supported with the provision that they be made readily available to other researchers. Costs for such approved research resource components would be provided on a scale up to that of the main project.

7059 NATIONAL GENE VECTOR LABORATORIES (NGVL)

FY 2002 Action
In FY 2001, NIDDK joined the National Center for Research Resources, the National Cancer Institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Neurological Disorders and Stroke, the National Institute of Child Health and Human Development and the National Institute of Allergy and Infectious Diseases in RFA, RR-01-002 to recompete the NVGL. The NGVL were established in 1995 to produce clinical grade vectors for human gene transfer protocols. The purpose of this Request for Applications (RFA) is to continue the support of the NGVL to produce and distribute such vectors and to perform related toxicology studies for Phase I and II human clinical gene transfer protocols. These grants were awarded in FY 2001. Each participating Institute supports the vector production or the toxicity studies for grants supported by that Institute. Funds are being set aside in FY 2002 to support studies from NIDDK supported investigators that are approved by the NGVL Steering Committee.

Background
Advances in the fields of molecular biology and genetics have led to the identification and characterization of many genes and their products. As a consequence, over 400 gene transfer clinical protocols have been initiated in the U.S. during the past decade. Specific gene transfer studies have addressed single gene disorders such as cystic fibrosis, severe combined immune deficiencies, hemoglobinopathies, hemophilia, hyperlipidemia, multifactorial disorders such as cancer and heart disease, and infectious diseases such as acquired immunodeficiency syndrome (AIDS). While the promise of gene transfer was viewed as great, the technical requirements and the expense of vector development, production, and safety testing limited the capacity of clinical investigators to proceed with implementation of many protocols. The unavailability of vectors constituted a barrier to progress in the field of gene transfer.

In response to these needs, the NGVL was established as a cooperative national effort to produce and distribute vectors for human gene transfer studies. The availability of the resources provided by these facilities lowered the cost barrier posed to investigators for the production of vectors and generated vectors for rare disorders for which there was little commercial interest. The NGVL Coordinating Center was also established in 1995 and is located at the Indiana University. It is responsible for organizing the meetings of the NGVL Review Committee and Steering Committee, receiving investigator requests for NGVL services, oversight of compliance with the NGVL Policy and Procedures document (http://www.ngvl.org/), maintenance of the Toxicology Database, post-distribution monitoring and other administrative issues. Indiana University is also the site of an existing NGVL Production Facility that generates retroviral vectors.

Research Goals and Scope
The objective of this RFA is to expand this national infrastructure by inviting applicants to become part of the NGVL network. Awardees will then be designated either as Production Facilities to construct, produce and distribute vectors for Phase I and II human gene transfer protocols or as Toxicology Centers to generate and share toxicology data relevant to particular gene vectors for such protocols.

7060 ANCILLARY STUDIES ON THE EFFECT OF THE USE OF CONTROL GROUPS IN CLINICAL TRIALS

FY 2002 Action

This is a Program Announcement (PA) for grants which will use the patient population within existing NIH-funded interventional clinical trials to conduct ancillary studies which will address the biological, behavioral and statistical issues related to the use of a control or comparison group within that trial and the effects of inclusion of a placebo group on clinical trial design.

Background

The use of placebo controls has raised a number of ethical, philosophical, statistical, and trial design issues. Many of these issues were highlighted at the National Institutes of Health workshop "Science of the Placebo: Towards and Interdisciplinary Research Agenda" held in November 2000 (http://placebo.nih.gov). There is broad unanimity in the principle that in the conduct of clinical trials the inclusion of a placebo group is compatible with equipoise when there is no established treatment available. Implementation of this principle, however, requires complex judgments of benefit and risk about which there is frequently not general agreement. A more rigorous basis is needed to inform the selection of the appropriate control group in clinical trials. There are currently no funded studies or initiatives to address these issues.

Research Goals and Scope

The purpose of this PA is to fund studies which will utilize the patient populations in existing NIH-funded clinical trials to address the numerous issues and unresolved questions in clinical trial design which are involved in selecting and using a control group in clinical trials. Appropriate topics for investigation would include: (1) studies which address the magnitude of the placebo effect anticipated at various time points and with various study instruments and the effect on trial design; (2) the use of control groups in surgical interventions; (3) the magnitude of the placebo effect in various diseases; (4) the relationship between the size of the placebo effect and outcome measures, especially those which use patient self-report of response to therapy; (5) the relationship between placebo effect and regression to the mean; (6) the duration of the placebo effect; (7) patient factors that are predictive of the magnitude of the placebo effect; and (8) the development of novel study designs to isolate and measure the placebo response on various types of outcome measures and various times during conduct of the trial. It is anticipated that the results of the studies funded through this PA will provide new insights into the role of the placebo and control group in clinical trials and will provide better methods for trial design and analysis.